

REVIEW

Opportunities With Combined Modality Therapy for Selective Organ Preservation in Muscle-Invasive Bladder Cancer

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Combined-modality therapy for organ preservation represents an appropriate alternative to radical surgery in the management of several malignant diseases. The standard therapy for muscle-invasive bladder cancer in the United States has been radical cystectomy. Although the sequelae of radical surgery have been ameliorated somewhat by techniques for the construction of orthotopic bladders, the ideal therapy should both cure the patient of cancer and maintain a functioning natural bladder. Years of experience in Europe and Canada with bladder preservation using radiation therapy are documented. Advances in transurethral surgery technique and in the combination of radiation and chemotherapy have led to safe and effective regimens for patients with bladder cancer. Several recent trials with combined-modality therapy have established this treatment as a viable alternative to radical cystectomy in selected patients.

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INTRODUCTION

Transitional cell carcinoma of the bladder will be diagnosed in an estimated 50,000 Americans in 1996 and will cause 11,000 deaths [1]. While the treatment of choice for invasive bladder cancer in much of Europe and Canada is radical radiation therapy, conventional management of invasive bladder carcinoma in the United States over the past decade has involved radical cystectomy as the usual initial intervention, with or without subsequent adjuvant therapy. Radical cystectomy involves removal of the bladder and prostate in men and, in women, the removal of bladder, uterus, and anterior vagina. Urinary diversion is usually accomplished through an ileal conduit with urostoma in the abdominal wall. The recent evolution of multiple continent and orthotopic urinary bladder diversions, however, as well as nerve-sparing procedures to help preserve male potency, have made cystectomy some-

what less "radical" for the patient's quality of life. Whereas cystectomy has been successful at eradicating local disease for most patients, if bladder preservation could be achieved without altering survival or interfering with bladder function, it would be the ideal solution for the problem of invasive bladder cancer.

Combined-modality therapies for organ preservation have become standard in the modern management of many malignancies. Significant changes in the approach of cancer specialists have led to commonplace use of conserving therapies for breast cancer, sphincter-sparing approaches for anorectal cancers, voice preservation in

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laryngeal cancers, and limb-sparing methods in sarcomas of the extremities. These approaches have been shown to achieve equivalent (or superior) results as compared to conventional radical surgical approaches, with improvement in functional preservation and quality of life.

The primary goal of any organ-preserving therapy must always be patient survival. If an organ-preserving approach can maintain function and be shown to have equivalent survival, such an approach should be considered an appropriate alternative to radical surgery. It is now evident that radical surgery may not be necessary for cure in selected groups of patients with invasive carcinoma of the bladder. Combined-modality therapy for bladder preservation is a viable alternative for patients with favorable tumors. Several recently published studies [2–7] show that selective bladder-sparing approaches combining conservative surgery, radiation therapy, and chemotherapy offer survival rates equal to those achieved with cystectomy (50–70%), while achieving a normal functioning bladder in virtually all patients.

The evolution of bladder preservation approaches has involved trials of monotherapies, either limited surgery or radiation therapy alone. There have also been several attempts at successful bladder preservation with two-modality approaches: combining limited surgery with either radiation or chemotherapy. These approaches have shown efficacy in achieving local tumor control with bladder preservation, but with less success in matching the survival rates achieved with radical surgery. Recent reports, however, have established multimodality therapy, combining limited surgery, systemic chemotherapy, and external beam radiation therapy, as the preferred model for successful bladder preservation.

RESULTS OF ORGAN PRESERVATION WITH MONOTHERAPY

Limited Surgery

Partial cystectomy. Open partial cystectomy is rarely practiced in the current management of bladder cancer, primarily because historic analysis has shown a high rate of local and pelvic relapse and because endoscopic methods of resection have proven to be equally effective. The procedure, which includes full-thickness resection of the tumor and bladder wall, was perceived as a means of preserving function while avoiding the hazards of major surgery.

Sweeney et al. [8] reviewed the literature, including 10 published series involving more than 500 cases, which argued that 5.8–18.9% of patients with muscle-invasive bladder cancer could be reasonably treated with partial cystectomy. Local recurrence rates ranged from 38% up to 78%, however, showing that this method is an unacceptable approach for most patients. Fifty percent of the local recurrences appear within 1 year and two-thirds by 2 years. Five-year survival rates of 75–100% for grade 1 tumors, 46–75%

for grade 2 tumors, and 22–55% for grade 3 tumors are reported. By stage, Ta tumors show 100% 5-year survival; T1, 58–80%; T2, 29–82%; T3a, 14–62%; T3b, 0–33%; and T4, 0–20% [9–13].

Transurethral resection of bladder. Improvements in both equipment and surgical techniques have advanced endoscopic methods of bladder tumor resection as a suitable alternative to open surgical procedures. Transurethral resection of the bladder (TURBT) is appropriate for all bladder tumors except for those occurring high on the posterior wall or in the dome of the bladder. Overlying peritoneum at these sites makes full thickness resections hazardous.

No randomized studies have compared TURBT alone with cystectomy or other therapy. Retrospective studies support that TURBT alone may be appropriate for highly selected patients with small tumors of favorable grade. Barnes et al. [14] reported 27% 5-year survival in 85 patients with well-differentiated or moderately differentiated T2 transitional cell carcinomas treated with TURBT alone.

Herr [15] reported on 45 patients from a population of 217 with invasive bladder cancer who could be appropriately managed with TURBT alone. The study included 37 patients staged T2, 7 staged T3, and 1 staged T4a. Selection for TURBT was made based on negative ($n = 20$) or superficial ($n = 25$) residual after initial TURBT, as well as negative urine cytology. Overall survival of this selected subgroup was 82% at a median follow-up of 61 months. Thirty-four or 76% of the selected 45 or 16% of all 217 treated patients retained their bladder.

Henry et al. [16] reported a selected series of TURBT alone for 43 favorable patients. All were T2 ($61\% < 3$ cm). Thirty-three of 43 (77%) remained disease free in the retained bladder at a follow-up of 5 years. Solsona et al. [17] selected patients for TURBT alone if resection was visibly and palpably complete and if biopsies were negative from the floor and margins of the resection. Thirty-one of 59 (53%) remained tumor free in the bladder at a mean follow-up of 55 months. Twelve recurrences were superficial; overall 43 of 59 retained a bladder free of invasive recurrence. Overall survival was 83%. A 5-year follow-up report found no progression in 42.4%, progression in 32%, bladder preservation in 40.7%, and a 5-year disease-free survival of 78% [18].

Chemotherapy

A limited number of recent trials have analyzed the treatment of invasive bladder cancer with chemotherapy alone. Because of low rates of complete response (CR), strategies have evolved into induction regimens before definitive surgery or radiotherapy, rather than radical chemotherapy alone. These trials show a complete response rate of about 25%, achieved with regimens typically com-

TABLE I. Results of Treating Bladder Cancer With Radiation Alone

Series	No. of patients	Clinical stage	5-year survival (%)	5-year local control (%)
London Hospital [30]	182	T2-T3	40	41
UK Cooperative Group [27]	157	T3	23	45
Princess Margaret Hospital [29]	121	T2-T4a	40	35
Prince of Wales Hospital [31]	342	T1-T4b	—	45
Belgium/Netherlands [35]	147	T2-T3	31	35

TABLE II. Randomized Trials of Radiation Therapy + Cystectomy Versus Radical Radiation Therapy and Salvage Cystectomy for Bladder Cancer

Treatment	Study	No. of patients	Clinical stage	5-year survival (%)	Distant metastasis (%)
50 Gy + cystectomy	A	35	T3	46	—
60 Gy + salvage cystectomy	A	32	T3	22	—
40 Gy + radical cystectomy	B	98	T3	39	—
60 Gy + salvage cystectomy	B	91	T3	28	—
40 Gy + radical cystectomy	C	88	T3	29	34
60 Gy + salvage cystectomy	C	95	T3	23	32
50 Gy + radical cystectomy	D	37	T2-T4a	27	38
60-68 Gy + salvage cystectomy	D	35	T2-T4a	40	31

A, M.D. Anderson Hospital [36]; B, U.K. Cooperative Group [37]; C, National Danish Trial [38]; D, National Bladder Cancer Group (S.D. Cutler, personal communication, Baltimore, MD).

binning methotrexate and cisplatin [19-24]. Survival with preserved bladder is noted in only 18-20% at 3 years [21].

Radiation Therapy

External beam radiation. Radical radiation therapy for muscle-invasive bladder cancer has been the standard treatment of choice in Europe and Canada for many years. An initial clinical complete response is achieved in 40-52% of cases using conventional fractionation to 55-65 Gy [25]. Of those who achieve a clinical complete response, however, one-fourth to one-third will experience local failure. Ultimately only 30% will maintain a tumor-free bladder after radical radiation alone. Several large retrospective series are available for evaluation of this approach [26-35] (Table I). Radical radiation has also been compared to radical surgery (with preoperative radiation therapy) in four modern randomized trials [36-39] (Table II).

The probability of durable local control with radiation therapy alone is determined, to a degree, by tumor factors such as size, stage, and histology, as well as by clinical factors such as presence of ureteral obstruction or the coexistence of carcinoma in situ [34]. Because bladder cancer is a heterogeneous disease, these factors cannot, by themselves, accurately predict response to radiation. For this reason, the typical approach for radical radiation has involved an evaluation for response early after therapy

to be followed by cystectomy in the absence of complete response.

Miller [36] reported on a small single-institution trial limited to patients with large T3 tumors comparing preoperative radiation therapy and cystectomy to radical radiation with salvage cystectomy. Thirty-five patients were randomized to receive radiation therapy followed by planned cystectomy. For these patients, the 5-year survival was 46%, as compared to only 22% for the 32 patients in the radical radiation therapy arm. The study has been criticized for its small size, slow accrual of patients (over 8 years), and the inclusion of large tumors, unlikely to be cured by radiation.

The Institute of Urology in London [37,40] conducted a prospective, randomized, multicenter trial comparing radical radiation therapy to 60 Gy (to be followed by salvage cystectomy in the absence of CR) versus 40 Gy of preoperative radiation therapy followed by cystectomy. The design of the trial was to prove the necessity of cystectomy in bladder cancer management. The trial, however, failed to find a significant difference in survival (5-year survival 29% for radical radiation therapy versus 38% for preoperative radiation therapy plus cystectomy).

The Danish Bladder Cancer Group [38] also found no difference in overall survival after a median follow-up of 50 months for 183 patients. There was, however, a much higher rate of pelvic recurrence in the radical radia-

tion therapy arm (36% vs 6.8%). Twenty-seven of 95 patients randomized to radical radiation therapy eventually underwent salvage cystectomy for recurrent tumor. The incidence of metastatic disease was similar in both groups (24% vs 32%). The persistence of tumor in the bladder apparently did not contribute to an increased rate of metastasis if salvage cystectomy was promptly performed.

A randomized trial of 72 patients was conducted by the National Bladder Cancer Group comparing 50 Gy followed by cystectomy with radical radiation therapy to 60–68 Gy (with salvage cystectomy for recurrence). No difference in 5-year survival (40% in the radical radiation therapy arm vs 27% for radiation therapy plus cystectomy) nor rate of metastasis (38% in radical radiation therapy arm vs 31% for radiation therapy plus cystectomy) was identified. Median follow-up was 66 months S.D. Cutler, personal communication, Baltimore, MD, 1983).

A U.S. Veterans Administration trial, criticized for its design and randomization method, compared cystectomy, radical radiation, and preoperative radiation followed by cystectomy [41]. No difference in survival was found in the three arms.

Of interest are investigations of altered fractionation schemas which have shown improved rates of clinical complete response. The Royal Marsden Hospital has treated patients with 1.8–2 Gy bid, 5 days/week, to doses of 57.6–64 Gy in 32 fractions over 26 days. Seventy of 85 patients entered in this trial had 3–6 months post-treatment cystoscopic evaluations. Of these, the clinical complete response rate was 80% [39,42]. A randomized trial of 168 patients with T2–T4 tumors unsuited for cystectomy was performed during the 1970s. In this study, hyperfractionated (not accelerated) radiation therapy delivered in 1 Gy fractions tid, to a dose of 84 Gy was compared to 64 Gy in 2 Gy QD fractionation. The hyperfractionated patients had improved survival at 5 years (27% vs 18%) and an improved CR rate (41% vs 25%), although neither finding reached statistical significance. The apparent improvement in outcome came at the expense of increased bowel complications [43].

In the published retrospective trials of radical radiation therapy, 5-year survival has ranged from 23% to 46% for patients with T2 and T3 tumors. These survival rates are somewhat lower than those for contemporary cystectomy series, perhaps the result of selection of cystectomy patients with less advanced disease and generally more favorable functional status. Radiated patients were staged clinically, possibly underestimating the extent of disease. Even given these limitations, however, the 5-year rate of maintaining a functional bladder, free of invasive recurrence, ranges from 35% to 45%, with a mean of 41% with radiation as monotherapy for patients with T2 and T3 tumors (Table I).

Brachytherapy. Although not widely practiced in the United States, interstitial brachytherapy has been used in Europe in combination with external beam radiation and conservative surgery with good results [44–47]. Careful selection of patients with solitary nonrecurrent tumors of stage T2 or T3a is the norm. Tumors of <5-cm diameter in patients who are fit for surgery and have adequate bladder capacity can be treated appropriately with this method. Treatment of such highly selected cases (one center considered only 10% of patients with invasive bladder cancer eligible [47]) yields local control rates of 75–80% and 5-year survival rates of 50–76%. Skill and experience with the techniques are paramount, and randomized trials are not available to assert superiority to limited surgery and external radiation.

Quality of life. In analysis of quality of life, the Danish Bladder Cancer Study group reported that patients randomized to preoperative radiation therapy and cystectomy had the largest reduction in their social and sexual activities for 18–24 months after therapy [48]. This was primarily due to dissatisfaction with urinary diversion and the loss of sexual function for 100% of the men. Such morbidity is notable when compared to patients receiving curative radiation therapy. Seventy-two Royal London Hospital patients were evaluated for bladder and rectal function following radical radiation to 60 Gy in 30 fractions [49]. They were compared to age-matched controls who had never received any radiation therapy and who had no known bowel or bladder disease. No difference in function or quality of life was identified.

RESULTS WITH LIMITED SURGERY AND CHEMOTHERAPY

Clinicians have long recognized that, regardless of local therapy, more than 50% of patients with invasive bladder cancer will die of metastatic disease within 5 years. For this reason, there has been support for the prompt use of systemic therapy in the overall bladder cancer management. A small number of trials of neoadjuvant chemotherapy and limited surgery in the interest of bladder preservation have been performed [50–60]. In highly selected groups of patients who had initial monofocal lesions and who showed a significant response to neoadjuvant therapy, bladder preservation seems feasible. High rates of local recurrence, even in short follow-up, argue that, even in these selected patients, neoadjuvant chemotherapy and limited surgery (either partial cystectomy or TURBT) result in survival with preserved bladder in only a minority of patients. (Table III).

RESULTS WITH COMBINED-MODALITY THERAPY (LIMITED SURGERY, CHEMOTHERAPY, AND RADIATION THERAPY)

We have seen that local tumor control of invasive bladder cancers is possible with conservative surgery alone,

TABLE III. Bladder Cancer: Survey of Complete Response Rates

Treatment	Study	No. of series	Total no. of patients	Complete responders (%)
Conventional RT alone ^a	[29-32]	4	721	45
Chemotherapy alone ^b	[19-21,50-52]	6	301	27
TURBT + chemotherapy ^b	[56-59]	4	225	51
TURBT + chemo- and radiation therapy ^b	[2-4,7]	4	218	71

^aFull-dose therapy.^bInduction or neoadjuvant doses only.

RT, radiation therapy; TURBT, transurethral resection of bladder tumor.

radiation therapy alone, or with systemic chemotherapy alone (Table III). Any of these therapies may be expected to achieve locoregional tumor control of only 20-40% in unselected patients. Control rates may be improved somewhat by combining radiation therapy or chemotherapy with limited surgery. These results are poor, however, when compared to local control rates, which approach 90% in most modern radical cystectomy series. With the primary goal of therapy being patient survival, and bladder preservation a secondary goal, an ideal bladder preservation regimen should achieve functional preservation without compromising survival rates achieved by radical surgery. Enhancing the pelvic control rate requires a more effective regimen than the monotherapy methods.

Recent years have seen the derivation of synergistic approaches combining systemic chemotherapy in combination with radiation therapy for many tumor sites. Several cytotoxic agents, particularly cisplatin and 5-fluorouracil, have been demonstrated to sensitize tissue to the effects of ionizing radiation [61-63]. Approaches combining local debulking surgery, chemotherapy, and radiation therapy in a rational and complementary fashion have evolved. Four major trials combining these modalities in clinically feasible regimens have strengthened the case for combined-modality therapy for bladder preservation.

Reports from the University of Erlangen in Germany [2], the University of Paris [3], the Radiation Therapy Oncology Group (RTOG) [6,7], and the Massachusetts General Hospital (MGH) [4,5] (Table IV) have established combined-modality therapy for bladder preservation as a viable approach to the management of invasive bladder carcinoma. Three of these studies have included aggressive transurethral resection with radiation therapy and a cisplatin-based chemotherapy regimen [2-4]. Three of these have incorporated an evaluation of response to induction chemo- and radiation therapy for selection of patients who go on to complete bladder preservation therapy (3-7).

Selection of patients for bladder preservation therapy should be based on the sound judgment of a well-coordinated team using urologic surgeons, radiation oncologists, and medical oncologists. Selection for bladder preserva-

tion is based on those prognostic factors that can be known before therapy [64]. The age and functional status of the patient, tumor size and stage, absence or presence of hydronephrosis, and the completeness of transurethral resection all have an impact on the choice and success of any bladder cancer therapy. Other important factors can only be determined on the basis of the outcome of induction therapy. Selecting patients based on response to induction therapy allows for cystectomy if significant residual disease is found. Negative biopsies and cytology following induction therapy supports continuation with consolidation therapy.

Results from several trials have shown that overall survival at 5 years is consistently around 52% (Table IV). Radical cystectomy trials show similar rates of survival, despite the exclusion from many published reports of approximately 15% of patients surgically identified as having metastatic disease. Cystectomy series are usually reported by pathologic stage, whereas bladder preservation trials may underestimate the extent of disease. Cystectomy patients also tend to be younger and in better general physical condition. A recent, thoroughly reported, modern cystectomy series reported a randomized study in which 122 patients underwent radical cystectomy between 1984 and 1989 [65]. The 5-year survival rate for clinically staged patients was 41% (48% for cT2), quite similar to reported bladder conservation trials. The MGH, RTOG, and University of Paris trials required re-evaluation with cystoscopy after radiation doses of only 24-40 Gy combined with chemotherapy. Patients at risk of failure can thereby be identified early and be considered for salvage cystectomy before delivery of radical doses of radiation. High rates of complete response have been achieved in all the trials, with percentages ranging from 70% to 80%.

It is of interest that the University of Paris regimen was initially planned as a precystectomy neoadjuvant study. The combination of cisplatin, 5-fluorouracil, and twice-daily high dose-per-fraction pelvic irradiation achieved a pathologic complete response in all of the first 18 patients treated with cystectomy. With no tumor found in the cystectomy specimens, the treatment plan changed

TABLE IV. Bladder Cancer: Results of Combined-Modality Trials

Series	Treatment	No. of patients	5-year survival (%)	5-year survival with bladder preservation (%)
Erlangen [2]	TURBT, cisplatin + XRT	79	52	41
MGH [5]	TURBT, MCV, cisplatin + XRT	106	52	43
RTOG-1 [6]	TURBT, cisplatin + XRT	42	52	42
RTOG-2 [7]	TURBT, MCV, cisplatin + XRT	91	62 ^a	44 ^a
Florida [66]	TURBT, MCV in all; cisplatin + XRT in 53%	94	51	18

^aFour-year data.

TURBT, transurethral resection of bladder tumor; XRT, external beam radiation therapy; MCV, methotrexate, cisplatin, vinblastine; MGH, Massachusetts General Hospital; RTOG, Radiation Therapy Oncology Group.

to one of selective bladder preservation. This was a significant improvement over the approximate 50% rate of clinical CR (and 25% pT0 rate) achieved with TURBT and chemotherapy alone. This report underlines the consistent observation of the value of radiation therapy in these bladder-preserving regimens: TURBT, chemotherapy, and radiation have 70–80% CR rates following induction. Importantly, 5-year survival figures with preserved functional bladder in trials with chemo- and radiation therapy of 36–44% are noted, as compared with only 33% at 30 months (18–20% at 5 years) in trials that omit radiation therapy.

Of the parameters used in measuring the success of a regimen of bladder preservation, perhaps most useful is the survival at 5 years with preserved bladder. This measurement considers the most important outcome—patient survival—as well as the success of therapy to maintain the bladder. Of the recently reported trials of combined-modality therapy, the 5-year survival with preserved bladder is consistently at 41–44% (Table IV). The exception is the report from the University of Florida, which found that only 18% of their patients treated with intention to preserve the bladder survived and maintained their bladders at 5 years [66]. This trial involved TURBT followed by MCV (methotrexate, cisplatin, vinblastine) chemotherapy in 94 patients. Of these, only 49 (53%) went on to receive radiation therapy with concurrent cisplatin chemotherapy. As complete response rates and bladder preservation results are consistently higher in those trials that include radiation therapy, the results from this series would not be expected to be representative of the potential for combined-modality therapy.

Tolerance to Combined Modality Therapy

The general argument that a fully irradiated conserved bladder is functionally unsatisfactory is in conflict with data from all of these trials. In the Erlangen study [2], only three cystectomies were necessary because of bladder shrinkage. This was from a population of 192 preserved bladders, for a rate of only 1.6%. A study of functional

quality of life in 72 radically irradiated bladder patients found no difference in urinary or rectal function as compared to age-matched and sex-matched controls [49]. Kachnic et al. [67] reported that a group of 21 women successfully treated with bladder preservation by chemo- and radiation therapy had 100% maintenance of continence without dysuria or hematuria at a median follow-up of 56 months; 91% noted unchanged or improved bladder function. There was no compromise in bowel or sexual function. An update of 106 patients treated at the MGH on protocols for bladder preservation was analyzed for functional results [5]. Seventy-five of the patients had bladder preservation following TURBT, 2 cycles of MCV chemotherapy, and 39.6 Gy of radiation with concomitant cisplatin. There were no patients who required cystectomy for shrinkage or bleeding at a median follow-up of 59 months.

Superficial Recurrences

Superficial bladder tumors may occur in 20–30% of patients who have had bladder preservation following multimodality therapy. Because carcinoma in situ may be understood as arising in a “field defect,” preserved bladder tissue retains the biologic propensity to form superficial tumors. These patients are amenable to traditional therapy, including transurethral resection and intravesical immunotherapeutic or chemotherapeutic agents. Eighteen patients of a population of 75 (24%) with initial bladder preservation at MGH developed either Ta or carcinoma in situ in the retained bladder [5]. Fourteen of these 18 have been maintained in remission by TURBT and intravesical therapy at a range of 15–49 months from the development of a new superficial tumor. This pattern further underlines the necessity of close follow-up evaluation of patients managed with bladder-preserving therapies.

CONCLUSION

Enough information now exists to offer bladder preservation as a treatment option to most patients with bladder

cancer. Combined-modality therapy is well documented as an alternative to cystectomy in the management of invasive bladder carcinoma, with information from multimodality and selective regimens reporting equivalent survival rates to cystectomy-based approaches. Importantly, 5-year survival rates with a preserved functional bladder of 36–44% are noted. The results are not acceptable in patients with hydronephrosis or in those with T3b–T4 tumors, but excluding these two groups of patients, 60–70% of patients entered into a bladder-preserving approach will achieve bladder preservation.

Once the myths associated with bladder preservation are dispelled, confirming that survival is not compromised, that delay in cystectomy does not result in an increased rate of metastasis, and that bladder function is excellent after bladder-preserving therapy, urologic oncologists should be convinced that bladder preservation constitutes appropriate treatment for selected patients with invasive bladder cancer, and patients will be encouraged to pursue organ preservation.

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